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DIAGNOSIS, TREATMENT, AND PREVENTION OF MALARIA

93-04535

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BACKGROUND

Many consider malaria to be the most important infectious disease in the world. It is estimated that 2.1 billion people live in areas of the world where malaria is transmitted, there are 100 to 300 million new cases of malaria, and 1 to 2 million deaths are caused by malaria every year.³⁰ In the past decade the severity of the malaria problem has worsened in many parts of the world because of resistance of parasites to antimalarials; resistance of the vectors, *Anopheles* sp. mosquitoes, to insecticides; socioeconomic problems that have led to a decreased capacity to optimally use existing tools to combat the disease; and movement of nonimmune populations into areas where malaria is transmitted.

Malaria exacts its greatest toll in the developing countries of the tropics and subtropics; however, the recent dramatic increase in international travel to countries where malaria is transmitted, including an estimated 7 million Americans per year (H. Lobel, personal communication, 1991), has led to malaria becoming a problem for many individuals who had thought the disease was wiped out. In fact, as many as 30,000 American and European travelers probably contract malaria every year.

Human malaria is caused by four species, *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, and *Plasmodium ovale*. *P. falciparum* accounts for 40% to 60% of the world's cases of malaria and probably more than 95% of deaths from malaria. *P. vivax* probably causes 30% to 40% of cases of malaria, while *P. malariae* and *P. ovale* are much less common. Among US travelers who

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develop malaria after return to the United States, about half acquire *P. falciparum* and the other half *P. vivax*.

LIFE CYCLE OF *PLASMODIUM* FOR THE CLINICIAN

Plasmodium sp. have a complicated life cycle in humans and *Anopheles* sp. mosquitoes (Fig. 1). Understanding the parasite life cycle will lead to provision of better advice to travelers and more optimal use of diagnostic tests and antimalarial drugs for treatment and prevention of malaria. Malaria is transmitted to humans by the bite of female *Anopheles* sp. mosquitoes that bite from dusk until dawn. The mosquito injects *sporozoites* that rapidly pass into the blood stream,⁵ and to the liver where they are thought to enter hepatocytes within minutes to several hours. Most of the uninucleate sporozoites develop within 7 to 14 days to mature *liver stage schizonts*, which in the case of *P. falciparum* have 10,000 to 40,000 uninucleate *merozoites*. This is an enormous asexual amplification process. After rupturing out of hepatocytes, each merozoite can invade an erythrocyte, where during the next 48 (*P. falciparum*, *P. vivax*, *P. ovale*), or 72 (*P. malariae*) hours each uninucleate merozoite can develop from a ring to a trophozoite and finally to a mature *erythrocytic stage schizont* with 10 to 35 merozoites. These erythrocytic stage schizonts then rupture releasing merozoites, each of which can then reinvade an erythrocyte initiating the cycle of amplification, rupture, and reinvasion that leads to increasing levels of parasitemia and the pathologic and clinical manifestations of malaria. There are no clinical manifestations associated with the sporozoite in the

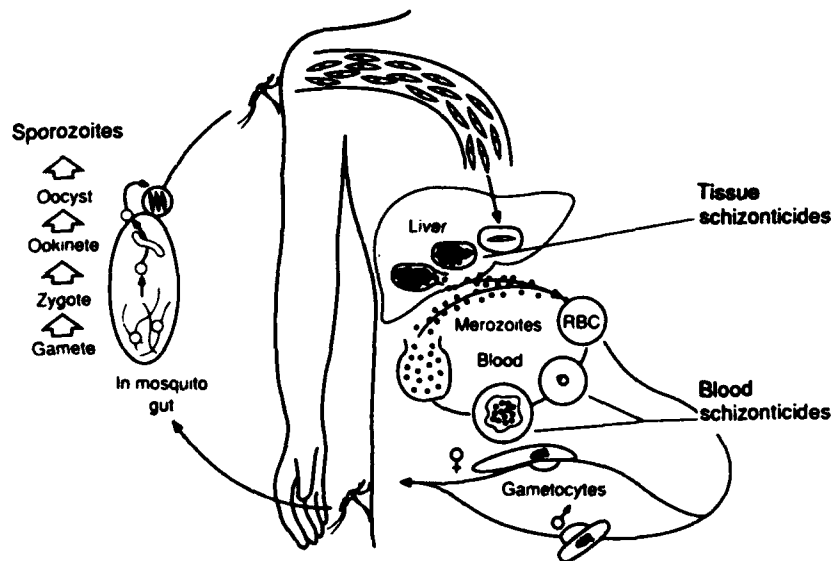


Figure 1. Life cycle of *Plasmodium* sp. (From Miller LH: Research toward malarial vaccines. Science 234:1349, 1986; copyright 1986 by the American Association for the Advancement of Science.)

circulation after inoculation by the mosquito, the parasite developing within the liver, or the merozoites released from the liver. Clinical manifestations only occur after rupture of infected erythrocytes, and they generally occur 10 to 14 days after an individual is bitten by the infected mosquito.

In *P. vivax* and *P. ovale* infections some of the sporozoites may not develop to mature liver stage schizonts for up to 2 years after inoculation; these forms of the parasite are called hypnozoites (sleeping forms).

Some of the parasites within infected erythrocytes do not develop to erythrocytic stage schizonts, but become sexual forms of the parasite called gametocytes. If a mosquito ingests blood infected with gametocytes, the gametocytes develop during an average of 14 days to sporozoites that can be inoculated into other humans. There are no clinical symptoms or signs associated with gametocytes.

TREATMENT OF MALARIA

Approach to a Patient

Optimal treatment of patients with malaria requires:

1. Rapid case identification.
2. Rapid parasitologic and clinical classification of the patient.
3. Initiation of therapy to rapidly reduce, and then eliminate parasitemia based on the parasitologic and clinical classification.
4. Initiation of supportive and ancillary therapy based on parasitologic and clinical classification.
5. Recognition of inadequate parasitologic or clinical response to therapy and development of complications, and initiation of appropriate therapy.
6. Recognition and treatment of recrudescence and relapse.

Rapid Case Identification (Diagnosis)

The clinician must suspect malaria, order appropriate diagnostic tests, and if the tests are negative, continue to order them every 12 hours for 36 to 48 hours.

Suspicion of Malaria

More than 99% of malaria infections are transmitted by the bite of malaria infected mosquitoes in the tropics and subtropics (Fig. 2, distribution of malaria). Anyone who travels to a malarious area, regardless of measures taken to prevent infection, is at risk of developing malaria. In the majority of patients symptoms and signs develop within 2 weeks of exposure and in 95% of cases within 6 weeks of exposure. In some cases, especially *P. vivax* infections, symptoms and signs may not appear for 2 to 3 years after exposure, however. *Any patient with a febrile illness who has been in a malarious areas during the past 2 to 3 years should be suspected of having malaria.*

During the past decade there have been a number of cases of malaria in Europe and the United States in individuals who had never left their native countries. In Switzerland, the United Kingdom, France, and Holland several of these cases have been attributed to malaria parasite-infected anopheline

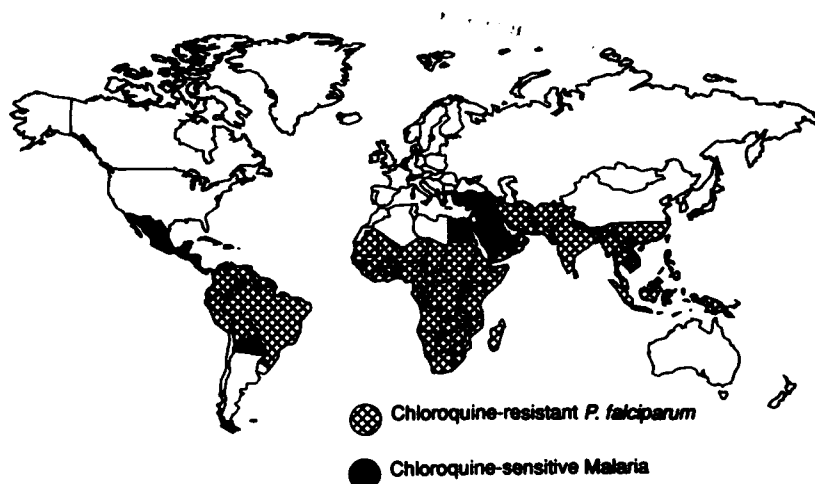


Figure 2. Distribution of malaria and chloroquine-resistant *P. falciparum*. (Adapted from Centers for Disease Control: Malaria. In Health Information for International Travel. Atlanta, 1991, p 98.)

mosquitoes carried into Europe on commercial airplanes arriving from Africa.²⁰ In the United States it has been different. Malaria was once transmitted in the United States from South Dakota to Florida, and although transmission was eliminated by the early 1950s, *Anopheles* sp. mosquitoes are still present in many areas. During the past 5 years there have been a number of cases of malaria in northern San Diego County, California,²⁰ and in 1991 there were two cases of malaria in central New Jersey, one in an 8-year-old boy and another in a 22-year-old woman, neither of whom had traveled to countries where malaria is transmitted (J. Zucker, personal communication, 1991). What probably occurred is that individuals acquired malaria in endemic areas, entered the United States, were bitten by *Anopheles* sp. in California and New Jersey, parasites ingested in the blood of these individuals developed to sporozoites within these mosquitoes, and the mosquitoes transmitted the infection to the unsuspecting residents of California and New Jersey. *Malaria must be suspected in any patient with a fever of unknown origin.*

Plasmodium sp. infection can also be transmitted by injection of the asexual, erythrocytic, disease-causing stage of the parasite. This occurs most commonly by blood transfusion, but can also occur among drug abusers who share contaminated needles. Malaria can also be transmitted congenitally. In the late 1970s and early 1980s there were a number of cases of congenital malaria among immigrants from Vietnam, Cambodia, and Laos.²¹

Diagnosis. Malaria is diagnosed by demonstrating parasites on Giemsa-stained blood films. Thick blood films are more sensitive than thin blood films because 20 to 40 times more blood can be examined in the same time. Thin blood films are used to determine the species of parasite.

If a blood film is negative it should be repeated every 12 hours for 36 to 48 hours. The primary reason for repeating blood smears is that *P. falciparum* parasites are only in the peripheral circulation for the first 18 to 24 hours of their 48 hour life cycle during the ring and early trophozoite stages. More mature trophozoites and schizonts are sequestered in the microcirculation of

the deep organs for at least half of the life cycle. If the infection is synchronous, that is, all parasites at the same stage of development, an individual with an extremely high level of infection might not have any parasites detected on blood smear because the parasites were at the trophozoite or schizont stage and sequestered in the microcirculation of the deep organs. Twenty-four hours later after the schizonts had ruptured and merozoites had reinvaded erythrocytes, however, the level of ring stage parasitemia could be extremely high, and the patient could have severe malaria.

There have been numerous attempts to improve on the blood smear, and although a number of techniques are promising, none has replaced the blood smear in clinical use. Acridine orange staining of centrifuged parasites in Quantitative Buffy Coat (QBC, Becton Dickinson) tubes is easy to perform and read, rapid, and slightly more sensitive than a thick blood smear.²² The disadvantages of this technique are: (1) it is expensive; (2) it requires a fluorescent microscope or an attachment to a standard light microscope; (3) it requires use of special tubes from a single manufacturer, and the tubes are optimally spun in a special centrifuge; (4) parasite concentration can only be crudely estimated; and (5) speciation is only 75% accurate.² Even with these disadvantages many experts, including this writer, believe that this technique is ideal for the rapid identification of patients with malaria, particularly in laboratories that handle only a very few malaria smears per year.

Another technique that holds great promise is the identification of specific parasite nucleotide sequences by oligonucleotide probing after polymerase chain reaction.²⁰ This technique is more sensitive than blood smear and acridine orange staining of centrifuged parasites but is currently not practical for the rapid diagnosis of most patients with suspected acute malaria. It may prove to be quite useful in the diagnosis of patients with suspected malaria whose blood smears are repeatedly negative. There has also been considerable work done using monoclonal antibodies to detect circulating malaria antigens.²⁰ Such techniques are currently at least 10 times less sensitive than a thick blood film and are not recommended for diagnosis of malaria in an individual.

Parasitologic and Clinical Classification

Having determined that a patient has malaria, the clinician must determine the species of *Plasmodium* that the patient is infected with, the geographic origin of the infection, the degree of parasitemia, and the clinical status of the patient. The clinician can then answer the critical questions: *What is the best drug for treating the infection? What is the best route for delivering the drug? Does the patient have severe or complicated malaria requiring treatment in an intensive care unit?*

Species

Identification of species is optimally done on a thin blood smear. It is especially important to know rapidly if the patient is infected with *P. falciparum*, because most malaria-associated complications and deaths are caused by this parasite, and in most cases it should *not* be treated with chloroquine. It is important to know if the patient is infected with *P. vivax* or *P. ovale*, because such patients will require treatment not only for their disease-producing blood stage infections, but also to eliminate hypnozoites from the liver, thereby preventing relapse.

Geographic Origin of Infection

Chloroquine resistant *P. falciparum* infections have been identified from all malaria transmission areas except the Caribbean (Haiti and the Dominican Republic), Central America, and the Middle East (see Fig. 2). Unless the clinician is extremely familiar with treating malaria from a certain area, all *P. falciparum* infections acquired in areas where chloroquine resistance has been identified should be treated with an antimalarial other than chloroquine. Chloroquine-resistant *P. vivax* has been documented on the island of New Guinea (Papua New Guinea and Irian Jaya, Indonesia) and the island of Sumatra, Indonesia.^{2, 23, 25} *P. vivax* infections contracted on these two islands should be treated with an antimalarial other than chloroquine, such as mefloquine, halofantrine, or pyrimethamine/sulfadoxine (P/S). All other *P. vivax* infections can be treated initially with chloroquine.

Percent Parasitemia

The percentage of erythrocytes parasitized should be determined. If more than 3% of erythrocytes are parasitized the patient should be diagnosed as having severe malaria and admitted to an intensive care unit (ICU). It is often difficult to detect low level *Plasmodium* sp. parasitemia, and diagnosis often requires examination of a thick blood smear: something that is quite difficult for the inexperienced microscopist. When the parasitemia has reached the 3% level any laboratory technician who is used to looking at thin blood films should be able to easily detect and count the parasites. The level of 3% is arbitrary; others use a cut-off of 5%.³⁶ What is clear is that as the parasitemia level increases, the chance of survival decreases.⁶

Definition of Severe Malaria

Any patient with malaria parasitemia who has an abnormal level of consciousness (*cerebral malaria*), greater than 3% parasitemia (*hyperparasitemia*); hematocrit less than 20% (*severe anemia*); hypoglycemia; renal, cardiovascular, hepatic, or pulmonary dysfunction; disseminated intravascular coagulation; prolonged hyperthermia; or high output vomiting or diarrhea is considered to have severe malaria. Such patients should be admitted to an intensive care unit (ICU), treated with intravenous antimalarials, considered for an exchange blood transfusion, and provided with standard ICU patient management.

CHEMOTHERAPY TO REDUCE AND ELIMINATE ASEXUAL PARASITES

Effective treatment requires a drug to rapidly reduce asexual blood stage parasitemia (a *blood schizonticide*). In some patients with *P. falciparum* a second blood schizonticidal drug is required to eliminate all parasites from the blood stream and thereby achieve clinical cure. Patients with *P. vivax* and *P. ovale* infections who have been clinically cured generally must be treated with primaquine phosphate, a *tissue schizonticide*, to eliminate all liver stage parasites and achieve *radical cure* of the patient (elimination of all asexual parasites from the body).

Formulations, Resistance Patterns, and Side Effects and Precautions for Specific Antimalarials

Chloroquine

Formulations. Chloroquine is available in the United States in 500 mg tablets of chloroquine phosphate (300 mg chloroquine base) (Aralen), and in generic 250-mg chloroquine phosphate (150 mg base) tablets. Chloroquine hydrochloride is available for parenteral use in 5-mL ampoules containing 50 mg/mL of the salt (40 mg/mL chloroquine base).

Resistance Patterns. Chloroquine-resistant *P. falciparum* has been reported from all malarious areas of the world, except the Caribbean, Central America, and parts of the Middle East. Chloroquine-resistant *P. vivax* has been reported from Papua New Guinea, Irian Jaya, and Sumatra, Indonesia.

Side Effects and Precautions. Toxic manifestations are uncommon and mild with oral doses used for treatment of malaria, and when studied in placebo controlled double-blind trials often occur at the same frequency as after placebo. They include nausea, vomiting, dizziness, headache, blurred vision, fatigue, diarrhea, confusion, and seizures. Pruritus has been frequently reported in black Africans living in or out of Africa. It is much less common among whites. Chloroquine is a vasoactive drug, and its toxicity is determined by the rate at which it enters the vascular space. Thus, small doses administered by rapid intravenous bolus can be extremely dangerous, as can large intramuscular doses (10 mg/kg). Such treatment has been associated with hypotension, acute circulatory failure, and respiratory and cardiac arrest. To avoid this toxicity is preferable to give parenteral chloroquine by continuous infusion or by low dose intramuscular injection (3.5 mg/kg every 6 hours).³⁴ Chloroquine is considered safe in pregnancy.

Mefloquine

Formulations. Mefloquine is available in the United States as Lariam tablets (250 mg salt = 228 mg base). The combination of pyrimethamine/sulfadoxine (Fansidar) and mefloquine, called Fansimef, is available in some countries of Europe and Thailand, but not in the United States. Fansimef is not recommended.

Resistance Patterns. Mefloquine-resistant *P. falciparum* has been reported from Indonesia, Thailand, and a number of countries in Africa. With the exception of the Thai-Burmese border area where the cure rate was only 73%,¹⁸ and the Thai-Cambodian border where resistance has been reported to be even higher, resistance has been either sporadic or low (5% to 20%).

Side Effects and Precautions. When studied in double-blind controlled trials, the incidence of side effects associated with the use of mefloquine has not been much higher than the incidence associated with placebo or other antimalarials. Nonetheless there are now many case reports of side effects ranging from dizziness, gastrointestinal disturbances (nausea, vomiting, diarrhea, abdominal pain) and self-limited sinus bradycardia, to seizures, acute psychoses, agranulocytosis, and Stevens-Johnson syndrome.^{7, 39} Mefloquine is not recommended for chemoprophylaxis in individuals who are taking drugs that affect cardiac conduction (particularly beta-blockers and quinidine), individuals such as pilots who require fine motor skills and spatial discrimination, individuals with a history of seizures or psychosis, and in children less than 15 kg or in pregnant women. Its use for the treatment of malaria will depend on the risk of the drug versus the risk of inadequately treated malaria, and

with mefloquine the risk of malaria is almost always more significant than the risk of side effects. Nonetheless if used in any of these groups, the patients must be monitored closely.

Pyrimethamine/Sulfadoxine

Formulations. P/S is available in the United States in a single formulation, Fansidar. Each tablet contains 500 mg sulfadoxine and 25 mg pyrimethamine.

Resistance Patterns. P/S-resistant *P. falciparum* has been reported from most malarious areas of the world. With the exception of Thailand, however, the prevalence of P/S-resistant *P. falciparum* has generally been only low to moderate (5% to 30%). *P. vivax* infections generally clear more slowly after treatment with P/S than after treatment with chloroquine, but this drug combination clears most *P. vivax* parasites from the blood stream.

Side Effects and Precautions. P/S is generally extremely well tolerated, when used for treatment or chemoprophylaxis of malaria. Its use can be associated with all known side effects of sulfa drugs and pyrimethamine. The major concern with P/S has been severe cutaneous reactions (erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis) which was calculated to occur in 1/11,000 to 1/25,000 Americans taking Fansidar for chemoprophylaxis.¹⁶ Most fatal reactions were in individuals who took additional doses of the drug after onset of skin symptoms. The incidence of such reactions after treatment of malaria infections is unknown but apparently much lower. Fansidar should not be administered to individuals with allergy to sulfa drugs. It is not recommended for infants less than 1 month of age. It has been used for treatment of malaria in pregnancy without adequate data to establish safety, and is generally not recommended for chemoprophylaxis during pregnancy.

Quinine

Formulations. Quinine is available in the United States as quinine sulfate tablets and capsules for oral use. Ampoules of quinine dihydrochloride are available for parenteral use in some military treatment facilities but are not readily available to the general public.

Resistance Patterns. Quinine-resistant *P. falciparum* was first noted in Brazil in the early 1900s. In the late 1970s and early 1980s it was shown that although quinine alone rapidly reduced parasitemia in Thailand and some other parts of the world, it was often not adequate alone for completely eliminating all *P. falciparum* parasites from the blood stream, and an additional antimalarial such as doxycycline, Fansidar, or even clindamycin had to be used with quinine. Nonetheless, intravenous quinine infusion remained the drug of choice for initial treatment of severe malaria because this regimen always led to rapid reduction of parasitemia. In recent years, however, reports from Southeast Asia, especially Burma and Thailand,¹² indicate that in some patients with severe malaria there is no reduction in parasitemia after initiation of quinine infusion. This ominous finding is now being closely monitored.

Side Effects and Precautions. Serious side effects are infrequent, but minor side effects are common. It has a bitter taste. Headache and tinnitus are the most common side effects. Cinchonism, which includes tinnitus, headache, nausea, vomiting, abdominal pain, blurred vision, transient loss of hearing, vertigo, and tremors, often occurs during the first 2 or 3 days of therapy, sometimes subsides spontaneously, and virtually always disappears after dis-

continuation of the drug. Quinine has been reported to cause drug fever,²⁴ and is a local irritant. The most serious side effects are associated with rapid injection of a large dose. They include convulsions, hypotension, heart block, ventricular fibrillation, and death. When quinine is administered by slow intravenous infusion or orally, these life threatening side effects are exceedingly rare, and the only side effects are minor electrocardiogram (ECG) changes (lengthening of the QT interval and T wave flattening). Quinine has been thought to be an abortifacient, but recent data suggest that it is not.¹⁴

Quinidine

Formulations. Quinidine, the dextrorotatory diastereoisomer of quinine is widely available in the United States as quinidine gluconate for parenteral use.

Resistance Patterns. Resistance to intravenous infusion of quinidine gluconate for treatment of severe malaria has not been established.

Side Effects and Precautions. Quinidine is a drug with established activity on cardiac conduction and is well known, like quinine, to cause cinchonism (see "Quinine" above). Patients' circulatory status should be carefully monitored, and they should be frequently evaluated for evidence of cardiac arrhythmia, prolongation of the QT interval, and widening of the QRS complex. Quinidine levels in the therapeutic range are generally not associated with any serious toxicity, and the ECG findings may predict potentially toxic levels of the drug.

Doxycycline

Formulations. Doxycycline is available from a number of companies in both capsule and tablet formulations.

Resistance Patterns. Studies have been conducted in Thailand using doxycycline alone for chemoprophylaxis of chloroquine-resistant *P. falciparum* infections. It is not uniformly efficacious, but generally prevents greater than 90% of infections. It is less effective against *P. vivax*. Doxycycline has rarely been studied on its own for treatment of malaria because it is considered to be slow in onset of action. When combined with 7 days of quinine therapy cure rates can be expected to be 95% even in countries like Thailand with multidrug resistant *P. falciparum*. In Thailand when combined with only 3 days of quinine, however, efficacy rates have been as low as 60% indicating that doxycycline alone would not have acceptable efficacy rates.

Side Effects and Precautions. Candida vaginitis is a troubling and common side effect. Photosensitivity reactions are much less common, and esophageal ulcerations are a rare complication. Because of potential adverse effects on the teeth and bones of children and the fetus, doxycycline is not recommended for use in children less than 8 years of age or in pregnant women.

Primaquine

Formulations. Primaquine phosphate is available in the United States as tablets containing 15 mg base (26.3 mg salt).

Resistance Patterns. Strains of *P. vivax* vary in the susceptibility of their liver stages to primaquine. Some strains of *P. vivax* are relatively resistant to primaquine; patients continue to relapse after standard 14-day treatment. These individuals are then treated, generally successfully, with a double dose of primaquine. Such strains were originally described from the island of New

Guinea; however, they are now commonly found in Indonesia and other countries of Southeast Asia, and more recently have been described from Central and South America.

Side Effects and Precautions. Gastrointestinal side effects including nausea, vomiting, anorexia, dizziness, epigastric distress, and abdominal pain or cramps can be expected in 5% to 10% of adults receiving 15 to 30 mg primaquine base per day for 14 days. This can be reduced by ingestion of the drug with meals. Dose-dependent methemoglobinemia has been described with therapeutic doses, but is exceedingly rare.⁸ Primaquine can cause acute intravascular hemolysis through oxidant stress in individuals with erythrocyte glucose-6-phosphate dehydrogenase (G6PD) deficiency, an inherited X-linked trait occurring most frequently in blacks of African descent, and persons of Mediterranean and Asian extraction. In most blacks who have 10% to 20% of normal G6PD activity, hemolysis is generally self-limited, and ceases when the drug is withdrawn. Mediterraneans and Asians may have 0% to 7% of normal activity, and hemolysis is more severe and potentially lethal, and may continue even after the drug has been withdrawn. Primaquine is not recommended for individuals with less than 10% normal activity, but can be given safely using a weekly regimen to blacks with 10% to 20% of normal activity. Primaquine should not be used during pregnancy.

Halofantrine

Formulations. Halofantrine (Halfan) is available as 500-mg tablets and as a suspension. It is not available in the United States.

Resistance Patterns. Halofantrine is generally effective for treatment of chloroquine- and P/S-resistant *P. falciparum* infections that are sensitive to mefloquine.⁴ Preliminary data suggest that mefloquine-resistant parasites are also resistant to halofantrine. In eastern Thailand, an area of increasing mefloquine resistance, halofantrine has had poor efficacy.⁴ The drug is not currently recommended for chemoprophylaxis.

Side Effects and Precautions. Clinical trials indicate that halofantrine is well tolerated, although low incidences of abdominal pain, pruritus, vomiting, diarrhea, headache, and rash have been reported. Halofantrine has been shown to be embryotoxic in animals, and is contraindicated in pregnancy. In animals it is secreted in maternal milk and is not advised for use in lactating women.

Proguanil (Chloroguanide)

Formulations. Chloroguanide hydrochloride (Paludrine) is not available in the United States. It is available overseas in 100-mg tablets.

Resistance Patterns. Proguanil is only used for chemoprophylaxis, not for treatment of malaria. Several years ago 200 mg daily of the drug appeared to be quite efficacious for preventing *P. falciparum* infections in East Africa. Efficacy has diminished in East Africa and cannot be expected to be any greater than 65% in West Africa. Its efficacy in other parts of the world has not been established.

Side Effects and Precautions. When used for chemoprophylaxis of malaria it causes few side effects except occasional nausea and diarrhea and mouth ulcers. It is considered safe for use in pregnancy.

Chemotherapy of Uncomplicated Malaria

P. malariae

There are no well-substantiated reports of resistance of *P. malariae* to chloroquine (Table 1). It is expected that all blood stage *P. malariae* infections

will be completely eliminated by treatment with chloroquine achieving *clinical cure*. Because individuals infected with *P. malariae* do not harbor hypnozoites, chloroquine treatment will eliminate all parasites from the body (*radical cure*). Adults receive an initial dose of 600 mg chloroquine base, followed by doses of 300 mg 6, 24, and 48 hours later, or 600 mg at 0 and 24 hours and 300 mg at 48 hours. Children are treated with 25 mg/kg chloroquine base during 48 hours. A 500-mg tablet of chloroquine phosphate (Aralen) contains 300 mg chloroquine base, and a 250-mg tablet of chloroquine phosphate contains 150 mg base. Mefloquine, 15 mg/kg salt, as a single dose or divided into 2 doses given 6 hours apart, is also effective.

P. vivax and *P. ovale*

There are no well substantiated reports of resistance of *P. ovale* to chloroquine, but since 1989 there have been a number of reports documenting chloroquine-resistant *P. vivax* on the island of New Guinea (both Papua New Guinea²³ and the Indonesian Province of Irian Jaya),² and a single case report of chloroquine resistant *P. vivax* in a US traveler to Nias, a small island just off the coast of Sumatra, Indonesia.²⁵ All infections with *P. ovale*, and all cases of *P. vivax* that were not acquired in New Guinea or Sumatra are treated with chloroquine as described above for *P. malariae*. Optimal treatment for chloroquine-resistant *P. vivax* has not been established. Mefloquine (15 mg/kg), however, will almost certainly be effective in clearing blood stage infections,⁴ as would sulfadoxine/pyrimethamine (a single dose of three tablets for an adult). Oral quinine sulfate, 10 mg/kg three times a day for 7 days, is less effective. Halofantrine, which is not yet available in the United States, is also effective in clearing the blood stages of *P. vivax*.⁴ It is recommended that children ≤ 40 kg, receive three doses at 6-hour intervals of 8 mg/kg halofantrine as an oral suspension, and that adults receive three doses at 6-hour intervals of 500-mg tablets of halofantrine.⁴ It is recommended that individuals with *P. falciparum* infections who have had little or no previous exposure to malaria receive a second course of therapy after 7 days, but it is unclear if *P. vivax* infections will require this second course.

Of the four species of *Plasmodium* that infect humans, only *P. vivax* and *P. ovale* have delayed development of liver stage parasites, and can present with a delayed primary attack 6 to 12 months after exposure to an infected mosquito, or a delayed secondary attack called a "relapse," even 2 to 3 years after clinical cure with a blood schizonticide. To ensure that the patient with *P. vivax* or *P. ovale* infection is "radically cured" of malaria (all parasites eliminated from the body), a drug that kills parasites within hepatocytes must be used. The only such drug available for general clinical use is primaquine phosphate. After determining the G6PD status (see primaquine above), adults are treated with 15-mg primaquine base daily for 14 days or 45-mg primaquine base per week for 8 weeks. Children receive 0.25 mg/kg per day for 14 days or 0.45 mg/kg per week for 8 weeks. A number of strains of *P. vivax*, especially those from Southeast Asia and New Guinea, are relatively resistant to primaquine. They frequently relapse after treatment with primaquine and must be treated with a double dose of 30 mg (0.5 mg/kg) primaquine base for 14 days.

P. falciparum

P. falciparum infections acquired in Central America, Mexico, Haiti, the Dominican Republic, or the Middle East can be treated with chloroquine like

Table 1. TREATMENT REGIMENS FOR SPECIFIC MALARIA INFECTIONS

Species	Disease Severity	Choice of Drug	Drug	Route of Administration	Initial Dose (mg/kg)	Other Doses (mg/kg)	Interval Between Doses (h)	Length of Treatment (d)	Comment
<i>P. falciparum</i>	Severe	Drug of choice	Quinine dihydrochloride*	IV infusion	20 (salt) (2-4 h)	10 (2-4 h)	8	3-7	Doses can be reduced where parasite is more sensitive. Oral quinine sulfate and doxycycline when tolerated.
	Severe	Drug of choice	Quinine gluconate	IV infusion	10 (salt) (1-2 h)	0.02 mg/kg/min	—	3-7	Oral therapy with quinine sulfate and doxycycline when tolerated.
	Severe		Artemether†	IM	4	2	2	24-48 h	Not available in the United States. Oral therapy with appropriate drug when tolerated.
	Severe	Certain of sensitivity to chloroquine	Chloroquine base	IV infusion continuous or IM or SC	0.83 mg/kg/h	—	—	30 h	When tolerated, oral chloroquine to total dose of 25 mg/kg (base) given.
<i>P. falciparum</i>	Uncomplicated	Chloroquine sensitive	Chloroquine base	Oral	3.5	3.5	6	36 h	When tolerated, oral chloroquine to total dose of 25 mg/kg (base) given.
		Depends on sensitivity	Pyrimethamine/sulfadoxine (P/S)	Oral	10	5-10	6-24	48 h	Total of 25 mg/kg given during 48 h.
			Quinine sulfate	Oral	P = 1.25 S = 25	None		Single	Three tablets for adults.
				Oral	10	10	8	3-7	More effective with doxycycline.

P. malariae. Infections acquired in areas with known chloroquine-resistant *P. falciparum* can be treated with a number of other drugs. Mefloquine, 15 to 25 mg/kg salt (the higher dose is used in areas like Thailand with increasing resistance to mefloquine and in children because they metabolize the drug more rapidly than do adults), is given as a single dose, or in two doses 6 hours apart. P/S, three tablets for an adult (25 mg/kg sulfadoxine and 1.25 mg/kg pyrimethamine), for children, is administered as a single dose. Quinine sulfate, 10 mg/kg three times a day for 7 days, is administered alone, with a single treatment dose of P/S or with 7 days' treatment with 100 mg doxycycline twice a day. When combined with doxycycline or P/S, most cases of falciparum malaria can be radically cured with only 3 days of quinine treatment. Halofantrine is quite effective against chloroquine-resistant *P. falciparum*; it is available in some European countries and in West Africa, but it is not available in the United States. It is recommended that children ≤ 40 kg receive three doses at 6-hour intervals of 8 mg/kg halofantrine as an oral suspension and that adults receive three doses at 6-hour intervals of 500-mg tablets of halofantrine; individuals with *P. falciparum* infections who have had little or no previous exposure to malaria should receive a second course of therapy after 7 days. A recent in-patient study in Bangkok demonstrated that the combination of oral mefloquine (1250 mg, approximately 25 mg/kg) and oral artesunate (600 mg during 5 days) was 100% effective whereas mefloquine alone cured 81% and artesunate alone cured 88% of patients.¹³ It should be recognized that none of these regimens can be considered to be completely effective. For example, in vivo resistance of *P. falciparum* to mefloquine was documented in Thailand, Indonesia, and West Africa shortly after introduction of the drug in the early 1980s,⁸ and the cure rate with mefloquine (18 to 25 mg/kg) was only 73% on the Thai-Burmese border in 1990.¹⁶ All patients must therefore be closely monitored (see below, clinical and parasitologic monitoring), and treated with another drug if resistance is demonstrated.

Chemotherapy of Severe Malaria

Regardless of the species of parasite identified on the blood smear, it should be assumed that any patient with severe malaria (see above for definition) is infected with *P. falciparum*, and preferably treated with intravenous quinidine, quinine, or chloroquine, or, where available, parenteral artemether or artesunate (see Table 1). Severe malaria acquired in Central America, Mexico, Haiti, the Dominican Republic, or the Middle East can be treated with intravenous chloroquine. Infections acquired anywhere else in the world are treated with quinidine or quinine. Quinidine is administered as a continuous infusion. The initial dose is 10 mg/kg of salt, followed by 0.02 mg/kg per minute.¹⁵ Quinine is given by slow intravenous infusion over 2 to 4 hours. A loading dose of 20 mg/kg salt is followed by 10 mg/kg every 6 hours. Quinine may also be administered intramuscularly using the same dosage schedule,³¹ although an alternative schedule also has been recommended: three doses of 10 mg/kg at 4-hour intervals followed by 10 mg/kg every 8 hours. Chloroquine is administered by continuous infusion at 0.83 mg/kg per hour of base. Optimal serum levels are 3 to 7 mg/L for quinidine and 10 to 15 mg/L for quinine. Levels of chloroquine and its major metabolite, desethylchloroquine, are best measured in whole blood; levels of 0.7 to 1.2 mg/L are appropriate while on a continuous infusion. Whole blood chloroquine levels are generally three times greater than serum levels and six times greater than plasma levels. Levels greater than 20 mg/L of quinine and 10 mg/L quinidine may be toxic.

Derivatives of the Chinese antimalarial qinghaosu (artemesinin) are now being used to treat malaria in China and some other countries in Asia, Africa, and South America but not in the United States. Virtually all data indicate that drugs such as artemether,³⁵ and artesunate clear parasitemia more rapidly than do chloroquine and quinine, clear parasitemia in patients with multi-drug resistant *P. falciparum* infections, are not associated with significant side effects, and only need to be administered once or twice a day. The data do not indicate that such treatment leads to reduced mortality as compared to chloroquine or quinine in patients with severe malaria infected with drug sensitive strains of *P. falciparum*. Furthermore, with most formulations a second antimalarial is generally needed to completely clear parasites from the blood stream. Artemether should be administered intramuscularly as an initial loading dose of 4 mg/kg, followed by 2 mg/kg every 24 hours until the patient is able to tolerate oral medication.³⁵ Artesunate is administered by the intramuscular or intravenous route every 12 to 24 hours, initial dose 2 mg/kg and subsequent doses 1 mg/kg (K. Arnold, personal communication, 1992). Rectal suppository formulations of artemisinin are also available.

Additional Treatment for Severe Malaria

General Supportive Therapy

The patient with severe malaria is optimally cared for in an ICU with strict monitoring of input and output and electrolyte balance so as to maintain adequate cardiac output and renal perfusion and to prevent fluid overload. This generally requires monitoring right heart or pulmonary artery wedge pressures. Patients are nursed on their sides with frequent suctioning. Hyperthermia is associated with seizures and a poor outcome, so temperature should be kept below 38.5°C with cooling blankets, fanning, sponging, and antipyretics.

Exchange Blood Transfusion

Numerous case reports now exist that suggest that exchange blood transfusion reduces mortality in patients with hyperparasitemia.^{15, 19} Most experts would recommend a 2x exchange blood transfusion (5 to 10 L for adults) for any patient with more than 15% of erythrocytes parasitized and for patients with greater than 5% parasitemia who have evidence of severe dysfunction of other organ systems.

Unproven Adjunct Therapies

Heparin, cyclosporine, high molecular weight dextran, and epinephrine have all been proposed as therapy for severe malaria, but none has been critically evaluated in controlled trials. Moderate³² and high doses⁹ of dexamethasone have been shown not to be of value, and preliminary data indicate that hyperimmune immunoglobulin does not reduce mortality (T. Taylor, personal communication, 1992). Monoclonal antibodies to tumor necrosis factor are being studied, and pentoxifylline has been recently proposed as treatment.¹⁰ Most experts do not recommend these adjuncts to antimalarial therapy.

Recognition, Prevention, and Treatment of Complications of Severe Malaria**Anemia**

Most malaria patients develop anemia primarily caused by hemolysis and bone marrow dysfunction. Specific treatment is not necessary in most patients who only require antimalarial therapy; however, if the hematocrit is less than 20% or is falling rapidly in a patient who is critically ill, blood transfusion is indicated. In many parts of Africa anemic patients must be transfused with blood that has not been checked for HIV status. In these cases the general condition of the patient and the response to oxygen and colloid infusion must be taken into account before administering a transfusion.

The anemia of malaria can be worsened by oxidant-induced hemolysis in individuals with G6PD deficiency. Individuals from population groups with a high prevalence of G6PD deficiency should be screened before being treated with primaquine. There is no evidence that treatment of G6PD-deficient patients with malaria with any other antimalarial induces clinically significant hemolysis, and none of the other antimalarials should be withheld because of concerns of G6PD deficiency.

Hypoglycemia

Plasma glucose levels less than 40 mg/dL (2.2 mM/L) occur in 5% to 30% of cerebral malaria patients.^{9, 27, 30} It is more common in patients who are pregnant, have hyperparasitemia, or are severely ill. It occurs before and after institution of quinine therapy. Clinical diagnosis is difficult in critically ill patients. Glucose levels should be monitored every 6 hours, and whenever there is clinical deterioration. Treatment is with 50% dextrose (1 to 2 mL/kg) followed by a 4-hour infusion of 10% dextrose; glucagon can also be used. If the glucose level is greater than 60 mg% after 4 hours the infusion is changed to 5% dextrose.

Seizures

Seizures are common in malaria patients. It is difficult to distinguish clinically between a seizure caused by malaria, a febrile seizure, and a seizure caused by hypoglycemia. Seizures are frequently recurrent and prolonged in patients with cerebral malaria, and a seizure in a patient with hyperparasitemia is often the first sign of rapid clinical deterioration. Seizures are treated with standard drugs and the temperature is kept below 38.5°C, hypoglycemia (an infrequent cause of seizures) and electrolyte balance excluded. Fluid balance is closely monitored because some patients with cerebral malaria, especially children, have been shown to have elevated cerebrospinal fluid (CSF) opening pressures, suggesting increased intracranial pressure.¹⁷ Among Thai patients with cerebral malaria, seizures were prevented by the prophylactic use of phenobarbitone, but there was no evidence that this altered outcome.³³ Nonetheless, many experienced clinicians prophylactically treat patients with cerebral malaria with an anticonvulsant.

Renal Failure

Renal failure may be associated with hypovolemia, hyperparasitemia, or intravascular hemolysis that leads to decreased renal blood flow, decreased

renal capillary blood flow, and hemoglobinuria (blackwater fever), respectively. All often end with acute tubular necrosis. In a patient with malaria, azotemia, and oliguria, hypovolemia must be excluded. Input, output, electrolytes, and right heart or pulmonary artery wedge pressures are monitored, and a fluid challenge undertaken. Treatment with a diuretic and then a vasopressor like dopamine that increases renal blood flow is tried. If unsuccessful, the diagnosis of acute tubular necrosis is made, and the patient is treated like any other patient with acute renal failure caused by acute tubular necrosis.

Only 20% of quinine and 35% of quinidine is cleared by the kidneys, and their clearances are not substantially altered by renal failure. Therefore, recommendations for treatment are unchanged. Plasma levels should be monitored. If these are not available and the patient is not improving after 48 hours of therapy, individual doses should be reduced by 30% and the electrocardiogram and blood pressure carefully monitored for evidence of toxicity. There is little information available on the use of chloroquine in renal failure. If it must be used, it should be used at standard dosage.

Pulmonary Edema

Pulmonary edema is an uncommon but frequently fatal complication of severe *P. falciparum* infection that is most often found in patients who also have hyperparasitemia (reviewed in reference 9). It resembles adult respiratory distress syndrome and it is likely, but unproven, that the primary abnormality is increased permeability of pulmonary capillaries. Most patients have normal pulmonary artery wedge pressures, but fluid management is critical in these patients. Treatment is like that of any critically ill patient with adult respiratory distress syndrome (ARDS). Corticosteroids have been proven to be neither harmful or helpful.

Pneumonia

Aspiration pneumonia is common in cerebral malaria patients who are unconscious and have frequent seizures and vomiting. Nursing the patient on his or her side, and administration of anticonvulsants and antiemetics may be helpful for prevention. Treatment is that of aspiration pneumonia.

Gram-Negative Sepsis

Gram-negative organisms are often cultured from the blood of patients with severe falciparum malaria. These unconscious patients have multiple intravenous lines and urinary catheters and sometimes have diarrhea. The source of infection may be similar to those of nosocomial infections in other severely ill patients; however, passage of organisms from the gut, through an intestinal wall subjected to the stress of microcirculatory obstruction by parasitized erythrocytes, is also possible. Any patient who is not responding to antimalarial therapy as expected should be investigated for bacteremia and empirical institution of antibiotic therapy considered.

Hypotension, Shock, and Myocarditis

Most malaria patients have low but normal arterial blood pressures, but postural hypotension is common. Postmortem findings on humans and studies in nonhuman primates indicate that myocardial microcirculatory obstruction

with parasitized erythrocytes is frequent (reviewed in reference 9). Even in patients with cerebral malaria, however, clinical or electrocardiographic evidence of myocarditis or myocardial ischemia is rare, as is marked hypotension with evidence of decreased organ perfusion. If severe hypotension is present, gram-negative sepsis, pulmonary edema, metabolic acidosis, gastrointestinal hemorrhage, hypovolemia, and splenic rupture should be suspected. Treatment with fluids, blood, or vasopressors may be required.

Splenic Rupture

This is an infrequent complication that is essentially the only fatal complication of *P. vivax* infection, but splenic rupture can occur with all malarias. Diagnosis is dependent on suspicion and demonstration of blood in the peritoneum.

Disseminated Intravascular Coagulation

Although chemical disseminated intravascular coagulation (DIC) is common, clinically important DIC with bleeding is rare in malaria patients. If encountered, it is usually found in patients with multiorgan failure and hyperparasitemia. Clinically significant DIC should be treated with fresh whole blood. The use of heparin is controversial, but is generally not recommended.

Assessment of Parasitologic and Clinical Response to Therapy

Clinical

Patients generally become afebrile and show clinical improvement within 48 to 72 hours of initiation of therapy. If there is no improvement or deterioration, inadequate drug levels owing to inappropriate therapy or poor absorption, high grade drug resistance, or development of a complication including hypoglycemia, renal failure, splenic rupture, aspiration pneumonia, pulmonary edema, gram-negative sepsis, and anemia should be suspected.

Parasitologic

Parasitemia detected on blood film may increase during the 6 to 12 hours after initiation of therapy but should be reduced by 75% within 48 hours. If parasitemia has not been reduced 75%, there has been inadequate drug absorption, inappropriate therapy, or high grade drug resistance. This is especially critical in patients with severe malaria. Until recently, intravenous quinine has been adequate for reducing parasitemia in patients with severe malaria, but inadequate clinical and parasitologic response to intravenous quinine has been reported from Thailand¹² and Burma. Likewise, because of parasite resistance, drugs such as mefloquine, doxycycline, P/S, and quinine cannot be expected to eliminate all parasites from the blood stream in all patients with uncomplicated malaria.

Diagnosis and Treatment of Malaria in Special Groups

Pregnant Women

Malaria is often more severe in pregnant than in nonpregnant women, and it is especially associated with higher levels of parasitemia and more

frequent hypoglycemia. Furthermore, there is an increased risk of prematurity, abortion, and stillbirth. It is therefore especially important to rapidly diagnose and treat malaria in pregnant women, and to closely monitor such women for the development of complications.

Uncomplicated malaria is treated with chloroquine when appropriate (non-chloroquine-resistant *P. falciparum* and *P. vivax*, see above). The choice of drug for uncomplicated chloroquine-resistant *P. falciparum* is more difficult because of the lack of data on long-term side effects of treatment of a single episode. There is no evidence that a treatment regimen of mefloquine or P/S has any adverse side effects on the fetus, but the experience is not large enough to conclusively demonstrate lack of adverse effects. Nonetheless, most experts are comfortable treating pregnant women with *P. falciparum* infections with P/S or mefloquine, since the risks of not administering appropriate treatment are high. Doxycycline is generally not administered to pregnant women because of the potential effects on the fetus. Pregnant women who are infected with *P. vivax* are not given primaquine because of potential toxicity to the fetus. They are maintained on chloroquine chemoprophylaxis once per week until after delivery and then treated with primaquine.

Complicated malaria is treated like all other cases of complicated malaria (see above). The issue of appropriate treatment to save the mother takes precedence over all other concerns. Quinine has long been thought to induce uterine contractions and abortion or premature labor. Ten women between 30 and 40 weeks' gestation with severe falciparum malaria, all of whom received standard doses of 10 mg/kg quinine, were evaluated in Thailand. No deleterious effects of quinine on uterine or fetal function were detected.¹⁴ Uterine and fetal function should be monitored during treatment, but inadequate treatment of malaria is more likely to lead to increased uterine contractions and adverse effects on the fetus than is quinine.

Young Children

Treatment of malaria in children is essentially the same as treatment of adults. Young children metabolize quinine and mefloquine more rapidly than do adults.⁹ They may require up to a 50% increase in doses of quinine during the last days of treatment, and although adults are generally treated with 15 mg/kg mefloquine, some advocate use of 25 mg/kg mefloquine for treatment of children.

Minimum Requirements for Diagnosis and Treatment in Areas with Limited Facilities

A health care provider who has mefloquine or halofantrine and an antipyretic can adequately treat virtually all patients with acute, uncomplicated malaria. Treatment of patients with severe malaria is best accomplished in a modern hospital with an ICU. Unfortunately, most patients with severe malaria are not treated in such facilities. Most patients with severe malaria can be adequately evaluated and treated in outlying hospitals with a basic set of supplies (Table 2). The most important component of therapy is rapid administration of an appropriate antimalarial.

Table 2. MINIMAL REQUIREMENTS FOR ADEQUATELY TREATING PATIENTS WITH MALARIA IN AREAS WITH LIMITED FACILITIES

<i>Uncomplicated Malaria</i>
Mefloquine or halofantrine and an oral antipyretic
<i>Severe Malaria</i>
Quinidine gluconate or quinine dihydrochloride (artemether or artesunate where available)
Intravenous fluids
Antipyretics; suppository or parenteral formulation may be required
Dipsticks to check blood glucose
50% dextrose
Blood for transfusion; ideally screened for HIV and hepatitis B
An anticonvulsant medication such as diazepam
A broad spectrum antibiotic that crosses into CSF: chloramphenicol or third generation cephalosporin
A parenteral antiemetic
Bladder catheters
Nurses trained to measure vital signs, input, and output and to suction, turn, and cool severely ill patients
A laboratory that can read malaria smears, measure hemoglobin concentration or hematocrit, and count cells in the CSF

PREVENTION OF MALARIA

General Approach

1. Assess risk based on itinerary and clinical condition of traveler.
2. Counsel regarding reduction of contact with *Anopheles* sp. mosquitoes.
3. Decide on appropriate antimalarials to be used for chemoprophylaxis or presumptive therapy.
4. Counsel regarding potential side effects and appropriate action of traveler.
5. Decide on requirement for terminal radical cure of liver stages of *P. vivax* and *P. ovale* with primaquine.
6. If fever develops, counsel regarding requirement to seek diagnosis and treatment.

Assessment of Risk

The health care provider must estimate the risk of acquiring malaria infection on the basis of the proposed itinerary, length of stay, style of travel, and risk of the disease to the traveler based on his or her condition.

Risk of Infection

Malaria is transmitted throughout the tropics and subtropics (see Fig. 2), but the intensity of transmission varies considerably. From 1980 to 1988 80% of *P. falciparum* infections in US travelers reported to the CDC were acquired in sub-Saharan Africa, 7% in Asia, 7% in the Caribbean and South America, and 7% in the rest of the world. In many parts of sub-Saharan Africa, during certain months, everyone is bitten by an *Anopheles* sp. mosquito carrying malaria sporozoites in her salivary glands every day. In other parts of the world where malaria is endemic, it may take 30 to 60 days of exposure before everyone is

bitten by an infected mosquito. Even in the areas of Africa with such high inoculation rates, there may be months of the year when malaria is not transmitted at all. Malaria is transmitted in many large cities in sub-Saharan Africa, but with the exception of Guayaquil, Ecuador, is not transmitted in the major cities of Central and South America. Likewise, although malaria is transmitted in many rural areas of Southeast Asia, it is not transmitted in Bangkok, Thailand; Kuala Lumpur, Malaysia; Jakarta, Indonesia; Singapore; Rangoon, Burma; Pnom Penh, Cambodia (M. Wolfe, personal communication, 1992); or central Manila, Philippines. Travelers who visit only these major cities are not at risk of developing malaria, and they do not require chemoprophylaxis.

Risk of Disease

There is a wide spectrum of clinical responses to malaria, but on average the risk to a healthy 20-year-old will be quite different than the risk to a 70-year-old with a history of underlying cardiac, renal, or pulmonary disease. An attack of malaria with its attendant microcirculatory obstruction in such an individual can lead to rapid deterioration of the underlying problems. Likewise, if a pregnant woman develops malaria there will be an increased risk of spontaneous abortion and premature delivery, and if a 6-month-old, nonimmune baby develops malaria, severe disease and death can develop quite rapidly.

Reduction of Contact with Anopheles Mosquitoes

Travelers should be advised that the best way to prevent malaria is not to visit an area where malaria is transmitted. *Anopheles* sp. mosquitoes feed from dusk until dawn. If travelers must visit such areas they should try to leave the area before dusk. Individuals at high risk of developing complicated malaria such as those with chronic diseases, pregnant women, and infants must clearly understand that the optimal method for preventing malaria is avoidance. Individuals can reduce their chance of being bitten by a mosquito carrying malaria sporozoites in her salivary glands by wearing protective clothing (long sleeves and pants), using insect repellants (a 35% nonabsorbable formulation of *N,N*-diethyl-metatoluamide (deet [Ultrathon, 3M] is optimal), spraying their rooms with pyrethrum-containing flying-insect sprays, spraying their clothing with permethrin (Permanone), staying in rooms that are screened, and sleeping under insecticide-impregnated bednets.

Chemoprophylaxis

Choice of a drug regimen for chemoprophylaxis will be dependent on the individual's itinerary, length of stay, age, pregnancy status, use of other medications, general medical history, activities, and estimation of the risk of side effects from the drugs versus the risk of developing malaria and the risk of developing complicated malaria (Table 3). With the exception of postexposure prophylaxis with primaquine (see below), all currently recommended regimens are to be taken for 4 weeks after leaving the malarious area.

Itinerary

In 1992 visitors to Central America, Haiti, the Dominican Republic, and malarious areas of the Middle East should take chloroquine (300 mg base for

Table 3. CHEMOPROPHYLAXIS OF MALARIA

Drug	Adult Dose	Pediatric Dose
Chloroquine phosphate (Aralen)*	300 mg base, once per wk	5 mg/kg base, once per wk (maximum dose 300 mg)
Mefloquine (Lariam)*	250 mg salt, once per wk	5 mg/kg salt, once per wk (maximum dose 250 mg)
Doxycycline*	100 mg, once per d	>8 yr of age, 2 mg/kg per d (maximum dose 100 mg)
Pyrimethamine/sulfadoxine†	one tablet per wk	1/10 tablet/5 kg/wk (maximum, one tablet)
Proguanil (Paludrine)*,‡	200 mg, once per d	4 mg/kg per d (maximum dose 200 mg)
Primaquine phosphate§	15 mg base/d for 14 d or 45 mg base/wk for 8 wk	0.3 mg/kg base/d for 14 d (maximum 15 mg) 0.9 mg/kg base/wk for 8 wk (maximum 45 mg)

*Chloroquine, mefloquine, doxycycline, pyrimethamine/sulfadoxine (Fansidar), and proguanil are taken for 1-2 wk before entering the malarious area, while one is in the malarious area, and for 4 weeks after departure from the malarious area.

†Pyrimethamine/sulfadoxine is generally not recommended for chemoprophylaxis because of the high risk of fatal skin reactions (see text).

‡Proguanil is not available in the United States.

§Primaquine is taken after departure from the malarious area.

adults, 5 mg base/kg for children, *weekly* for chemoprophylaxis. This is because there has so far been no documentation of chloroquine-resistant *P. falciparum* or *P. vivax* from these areas, and there has never been documentation from anywhere of chloroquine-resistant *P. malariae* or *P. ovale*. This recommendation will change if chloroquine-resistant malaria parasites are identified in one of these areas.

In 1992 visitors to all other malarious areas of the world should take a drug that is effective against chloroquine-resistant *P. falciparum*. For US travelers, the first line drug for such prophylaxis is mefloquine (250 mg for adults, 5 mg/kg for children, *weekly*), and the second choice is doxycycline (100 mg for adults, 2 mg/kg for children above age 8 [maximum, 100 mg], *daily*). If neither of these drugs can be used and if the individual is at high risk of becoming infected (based on itinerary and style of travel) and is at high risk of developing complications of malaria (based on underlying medical condition), P/S (Fansidar) (one tablet for adults, 1/4 tablet/15 kg for children, *weekly*) can be prescribed, recognizing that there is a risk of 1/11,000 to 1/25,000 of development of fatal Stevens-Johnson syndrome or toxic epidermal necrolysis.¹⁶ If none of these regimens are advisable and the individual is traveling to sub-Saharan Africa, *weekly* chloroquine should be prescribed and the individual should be instructed on how to obtain proguanil (Paludrine) 200 mg for *daily* administration. This regimen is expected to be no more than 65% effective. An alternative to these regimens, often recommended when the risk of infection is only moderate or low and the risk of developing complications is low, is for the traveler to take *weekly* chloroquine and at the first sign of fever to self-administer a treatment dose of P/S (Fansidar) (three tablets for an adult). Halofantrine (three doses of 500 mg at 6-hour intervals for adults) may replace P/S for this purpose when it becomes universally available. Some recommend mefloquine (15 mg/kg) in this situation, but it is currently less preferable because of concern regarding potential troublesome side effects.

Length of Stay

Short. The incubation period or time from being bitten by an infected mosquito and development of symptoms is a minimum of 8 days, but it is much more commonly 10 to 14 days. If an individual cannot take appropriate chemoprophylaxis, and within 10 days of first exposure to malaria he or she will be in a setting in which there is 24-hour access to excellent malaria diagnostic capabilities and physicians experienced in the diagnosis and treatment of malaria, then it is sometimes acceptable to not use chemoprophylaxis and rely on prompt diagnosis and treatment of malaria.

Long. Virtually no one who stays in malaria-endemic areas for years develops adequate acquired immunity to protect against infection with malaria. It is therefore necessary to continue taking malaria chemoprophylaxis. Both chloroquine and proguanil have been empirically shown to be safe when taken for periods as long as 10 or 20 years. There has been concern about adverse retinal effects of chloroquine after prolonged use, and it has been long recommended that individuals who take chloroquine for 4 to 6 years should have yearly ophthalmologic examinations. The total cumulative dose of chloroquine should not exceed 100 g. A recent literature review, however, suggested that such concerns are not well founded, and that these precautions are not necessary (M. Wolfe, personal communication, 1992). Tetracyclines have been taken for years for treatment of acne with no obvious long-term side effects, and although data are less complete for doxycycline, there is no indication that doxycycline is any less safe than tetracycline when taken for long periods. Mefloquine has only recently been introduced, and there is no such database available for mefloquine, but there are no data suggesting that prolonged use would be harmful. Although P/S has been in use much longer, there is no well-substantiated database demonstrating the safety or lack of safety of prolonged use. If the risk of infection is high or the risk of complications is high in areas with only moderate risk of infection, appropriate malaria chemoprophylaxis should be taken.

Age

Children share the same risk as adults of developing infection and disease, but as stated above, infants may be at greater risk of developing complicated malaria. Therefore, when appropriate, chemoprophylaxis is strongly recommended. Chloroquine and proguanil have been administered, apparently safely, to infants for many years. Unfortunately, chloroquine is manufactured in the United States only in tablets, although liquid preparations are available abroad. Proguanil is available only as a tablet. There is no reason to believe that mefloquine would be harmful to young children, but there are little safety data available on the use of mefloquine in young children, and the manufacturer therefore recommends the drug only for use in children greater than 15 kg. Doxycycline, like other tetracyclines, is not recommended for use in children < 8 years of age. Overdose of antimalarial drugs has been associated with many fatalities. The drugs should be stored in childproof containers out of the reach of children.

Pregnancy

Pregnant women should be counseled to avoid exposure to malaria. If they must visit a malarious area then they should take appropriate chemoprophylaxis. The risk of most drugs is likely to be greatest during the first trimester,

so female travelers should be counseled to try to avoid becoming pregnant while on malaria chemoprophylaxis. Those who have just become pregnant should be advised to defer travel plans until the second trimester.

Chloroquine and proguanil have been administered to pregnant women for many years with no observed adverse effects on the pregnancy or fetus. Women traveling to areas with chloroquine-sensitive parasites can take chloroquine.³⁷ The problem is travel to areas with chloroquine-resistant parasites. Doxycycline is generally contraindicated for malaria chemoprophylaxis during pregnancy. Adverse effects of tetracyclines on the fetus include discoloration and dysplasia of the teeth and inhibition of bone growth. No evidence exists that long-term chemoprophylaxis with mefloquine has adverse effects on pregnancy or the fetus; however, although the drug has been used safely for chemoprophylaxis of malaria among several thousand pregnant women (second and third trimester) in Malawi,³ the database is still not adequate to assure that it is safe. It is therefore not recommended for chemoprophylaxis in pregnancy. What can be done with a pregnant woman who must visit an area with intense transmission of chloroquine-resistant *P. falciparum*? Because of the potential serious outcome of even a mild episode of malaria, it is not appropriate to recommend presumptive therapy of a febrile illness with Fansidar or mefloquine. For sub-Saharan Africa that leaves the combination of chloroquine and proguanil, recognizing the fact that it will be no more than 65% effective, or advising mefloquine, which is not recommended by the manufacturer during pregnancy and for which there are inadequate safety data. Lastly, one could consider Fansidar, but in addition to the high rate of fatal skin reactions, the combination has been shown to be teratogenic in laboratory animals, and there is the potential late in pregnancy for sulfadoxine, like any other sulfa drug, exacerbating neonatal jaundice.

Primaquine should not be used during pregnancy because the drug may be passed transplacentally to a G6PD-deficient fetus and cause hemolysis in-utero. If a pregnant woman requires terminal prophylaxis to eliminate the dormant liver stages of *P. vivax* or *P. ovale*, she should receive weekly chloroquine chemoprophylaxis until delivery and then be treated with primaquine (see below).

Interactions with Other Medications and Vaccines

Chloroquine may interfere with the antibody response to human diploid rabies vaccine, if the vaccine is administered intradermally using the low dose (0.1 mL) regimen.

General Medical History

In formulating a plan for chemoprophylaxis the physician must take into account the general medical history. Individuals, particularly the elderly, with underlying chronic diseases are at risk of exacerbations of their underlying illnesses when they develop malaria. Thus, with an increased risk of disease, the requirement for providing the most effective chemoprophylaxis increases. Individuals with a history of seizures, psychiatric disorders, or cardiac conduction disturbances may be at increased risk of exacerbations of these conditions by antimalarials used for chemoprophylaxis, especially chloroquine and mefloquine (see below). Anyone with a history of sulfa allergy should not receive P/S.

Activities

Mefloquine is not recommended for travelers who must perform tasks that require fine coordination and spatial discrimination, such as airline pilots.

Side Effects

When compared with placebo in double-blind controlled trials, most of the side effects attributed to antimalarials are often found as frequently among individuals who receive placebo.

Chloroquine. Chloroquine rarely causes serious side effects at prophylactic doses. Headache, dizziness, blurred vision, pruritus, and gastrointestinal disturbances may occur. They rarely require discontinuance of chemoprophylaxis. Anecdotal reports exist that suggest that chloroquine may predispose to seizures in individuals with epilepsy. High doses of chloroquine for treatment of rheumatoid arthritis have been associated with retinopathy, and it is often recommended that individuals who have taken chloroquine chemoprophylaxis (300 mg base per week) for 4 to 6 years should undergo yearly ophthalmologic examinations; there are no solid data that support this recommendation, and in a recent review the authors concluded that it was not necessary (M. Wolfe, personal communication, 1992). Chloroquine may exacerbate psoriasis.

Mefloquine. Mefloquine rarely causes serious side effects at prophylactic doses; however, there have been numerous anecdotal reports of hallucinations and psychotic reactions, seizures, and nightmares associated with use of mefloquine for both chemoprophylaxis and especially treatment of malaria. Gastrointestinal disturbances and dizziness are also frequently reported. When studied in Peace Corps volunteers,¹¹ and in large groups of Swiss tourists,²⁶ however, with the exception of sleep disturbances, mefloquine has not been associated with any more side effects than has chloroquine.

Mefloquine is not recommended for individuals less than 15 kg (based on prudence, not data); travelers using beta-blockers or other drugs that may prolong cardiac conduction (based on structural similarities to quinine, quinidine, and other drugs that effect cardiac conduction and a single unpublished case that was associated with the use of mefloquine); or for travelers who must perform tasks that require fine coordination and spatial discrimination, such as airline pilots. It is also not recommended for travelers with a history of epilepsy or psychiatric disorders. As suggested above, the data supporting these relative contraindications to the use of mefloquine for chemoprophylaxis are not strong; nonetheless, these contraindications are listed in the drug package insert.

Doxycycline. The major concern with doxycycline is photosensitivity, which usually manifests as a severe sunburn-type reaction. This risk can be decreased by minimizing direct exposure to the sun, the use of sunscreens that absorb ultraviolet radiation, and by taking the drug in the evening. Doxycycline use can also be associated with *Candida* infections, especially vaginitis, nausea, vomiting, and diarrhea.

Pyrimethamine/Sulfadoxine. P/S (Fansidar) is well tolerated when used for chemoprophylaxis; however, its use for chemoprophylaxis has been dramatically reduced because between 1/11,000 and 1/25,000 individuals who take it develop fatal skin reactions (Stevens-Johnson syndrome or toxic epidermal necrolysis).¹⁶ It should never be used in individuals with allergy to sulfa drugs and anyone taking it who develops a rash should immediately discontinue use.

Proguanil. Proguanil rarely causes side effects at chemoprophylactic doses. Nausea, vomiting, and mouth ulcers have been reported.

Primaquine. The drug may cause severe hemolysis in individuals with

severe G6PD deficiency (see above). Its use is sometimes associated with gastrointestinal disturbances.

Risk-Benefit Ratio: Disease Versus Drug

The decision as to whether to recommend a drug for chemoprophylaxis is dependent on the *risk of infection*, the *risk of disease*, and the *risk and potential severity of side effects*. In the early 1980s a number of individuals who were traveling to Southeast Asia, where malaria is transmitted, but staying only in urban areas where malaria is not transmitted (risk of malaria, zero), inappropriately took P/S for chemoprophylaxis and died secondary to an allergic fatal skin reaction (risk of reaction, 1/11,000 to 1/25,000). These individuals should not have been taking any chemoprophylaxis. What about, however, the 55-year-old man traveling to rural West Africa for the 2-week trip he has been dreaming about for 15 years? He has a history of moderately severe chronic obstructive pulmonary disease and insulin-dependent diabetes mellitus, is taking a drug that affects cardiac conduction, and has a history of photosensitivity reactions with the use of tetracyclines. His *risk of infection* is high, and his *risk of disease* is high. His risk of developing a photosensitivity reaction while taking doxycycline is high; this reaction will undoubtedly spoil his trip and lead him to stop taking the drug but will probably not result in a life-threatening illness, and this risk can be reduced by using a sunscreensing agent. No data are available on the true risk of adverse cardiac effects after taking mefloquine, but the manufacturer does not recommend it for individuals on the cardiac drugs our traveler uses; the implication is that while the risk of side effects is unknown, there is the potential for a life-threatening response. What do we recommend? The first recommendation is not to go. The traveler insists, and is adamant that he will not take a tetracycline. After counseling the traveler regarding methods to reduce exposure, the physician is left with two options. The first is to prescribe chloroquine and recommend acquiring proguanil in Europe or Africa, knowing that it is probably only about half as effective as mefloquine, and because there is a high risk of infection, and a high risk of disease, the traveler has a good chance of developing a serious malaria infection. The second option is to advise the traveler of the potential risks of mefloquine (rate unknown) and the potential risks of malaria (rate high) and for the two of them to decide if this is appropriate for the traveler. Unfortunately such situations are becoming increasingly common, providing patient and physician with extremely difficult decisions.

REQUIREMENT FOR TERMINAL RADICAL CURE WITH PRIMAQUINE

Individuals who have had significant exposure to *P. vivax* or *P. ovale* should receive terminal prophylaxis with primaquine to eliminate dormant stages of the parasite, called hypnozoites, from the liver. After returning from a malarious area and establishing the level of G6PD activity (see above), adults with normal G6PD activity receive 15 mg primaquine base daily (0.25 mg/kg for children) for 14 days or 45 mg primaquine base (0.75 mg/kg for children) once per week for 8 weeks. The latter weekly regimen is well tolerated in individuals of African descent with moderate G6PD deficiency (10% to 20% of normal activity). It is not well tolerated in individuals, like those of Mediterranean and Asian descent, with low activity (0% to 7%) and should not be given to such

individuals. If there is a serious threat of relapse in such individuals, they can either rely on long-term chloroquine chemoprophylaxis, or on rapid diagnosis and treatment of febrile illnesses. Primaquine should not be administered to pregnant women (see earlier text).

The standard regimen of primaquine is not always effective in eliminating all liver stage parasites, and relapses may still occur, especially with infections acquired in Southeast Asia and on the island of New Guinea. If relapse does occur the patient can be treated with the appropriate blood schizonticidal drug and can then receive 30 mg primaquine base/day for 14 days (0.5 mg/kg for children).

ASSESSMENT AND TREATMENT OF ILLNESS WHILE TRAVELING AND AFTER RETURN

At this time no chemoprophylaxis regimen can be considered 100% effective. Therefore, any individual who is taking malaria chemoprophylaxis and who develops an illness with fever should be vigorously evaluated, and when appropriate, treated for malaria (see sections on diagnosis and treatment of malaria). Malaria chemoprophylaxis is recommended for 4 weeks after leaving a malarious area. This is because 95% of primary cases of malaria will manifest within 4 weeks of exposure. Relapses of *P. vivax* and *P. ovale* and some primary cases of *P. falciparum*, *P. vivax*, and *P. ovale* may first present with symptoms of malaria up to 2 to 3 years after exposure, however. Therefore, any individual with a febrile illness who has had potential exposure to malaria within the past 2 to 3 years should be evaluated for malaria. Individuals with fever who have returned from malarious areas should be advised to tell health care providers that they have traveled to a malarious area within the past few years, that they know that malaria is clinically indistinguishable from most other febrile illnesses, and that they demand to be evaluated for malaria for the next 48 hours.

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